

## REVIEW ARTICLE

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## Acute Myocardial Infarction

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**A**CUTE MYOCARDIAL INFARCTION WITH OR WITHOUT ST-SEGMENT ELEVATION (STEMI or non-STEMI) is a common cardiac emergency, with the potential for substantial morbidity and mortality. The management of acute myocardial infarction has improved dramatically over the past three decades and continues to evolve. This review focuses on the initial presentation and in-hospital management of type 1 acute myocardial infarction.

## DEFINITION AND TYPES

Acute myocardial infarction is an event of myocardial necrosis caused by an unstable ischemic syndrome.<sup>1</sup> In practice, the disorder is diagnosed and assessed on the basis of clinical evaluation, the electrocardiogram (ECG), biochemical testing, invasive and noninvasive imaging, and pathological evaluation.

Acute myocardial infarction is classified on the basis of the presence or absence of ST-segment elevation on the ECG and is further classified into six types: infarction due to coronary atherosclerosis (type 1), infarction due to a supply–demand mismatch that is not the result of acute atherosclerosis (type 2), infarction causing sudden death without the opportunity for biomarker or ECG confirmation (type 3), infarction related to a percutaneous coronary intervention (PCI) (type 4a), infarction related to thrombosis of a coronary stent (type 4b), and infarction related to coronary-artery bypass grafting (CABG) (type 5).<sup>1</sup>

## EPIDEMIOLOGIC FEATURES

The epidemiologic characteristics of acute myocardial infarction have changed dramatically over the past three to four decades (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Since 1987, the adjusted incidence rate of hospitalization for acute myocardial infarction or fatal coronary artery disease in the United States has declined by 4 to 5% per year.<sup>2</sup> Nevertheless, approximately 550,000 first episodes and 200,000 recurrent episodes of acute myocardial infarction occur annually.<sup>2</sup> Globally, ischemic heart disease has become the leading contributor to the burden of disease as assessed on the basis of disability-adjusted life-years.<sup>3</sup> Concurrently, the global burden of cardiovascular disease and acute myocardial infarction has shifted to low- and middle-income countries, where more than 80% of deaths from cardiovascular disease worldwide now occur.<sup>3,4</sup> Among 156,424 persons in 17 countries who were followed for an average of 4.1 years,<sup>5</sup> the risk-factor burden was directly related to income, with the highest burden of risk factors in high-income countries and the lowest burden in low-income countries. In contrast, an inverse relationship with income was noted for rates of acute myocardial infarction (1.92, 2.21, and 4.13 cases per 1000 person-years in high-, middle-, and low-income countries, respectively;  $P<0.001$  for trend). Mitigation of the high burden of risk factors in higher-income countries was attributed to greater use of pre-

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ventive measures and revascularization procedures.

#### PATHOBIOLOGIC FEATURES AND RISK FACTORS

The usual initiating mechanism for acute myocardial infarction is rupture or erosion of a vulnerable, lipid-laden, atherosclerotic coronary plaque, resulting in exposure of circulating blood to highly thrombogenic core and matrix materials in the plaque (see the Supplementary Appendix).<sup>6</sup> In the current era of potent lipid-lowering therapy, the proportion of cases in which erosion is the underlying cause is increasing as compared with the proportion of cases in which rupture is the underlying cause.<sup>7</sup> A totally occluding thrombus typically leads to STEMI.<sup>8</sup> Partial occlusion, or occlusion in the presence of collateral circulation, results in non-STEMI or unstable angina (i.e., an acute coronary syndrome without ST-segment elevation)<sup>9</sup> (Fig. 1). The occurrence of acute myocardial infarction in the absence of critical epicardial coronary disease is increasingly recognized (accounting for approximately 10% of cases of acute myocardial infarction). The various mechanisms underlying acute coronary syndromes, as well as risk factors for these disorders, are discussed in the Supplementary Appendix.

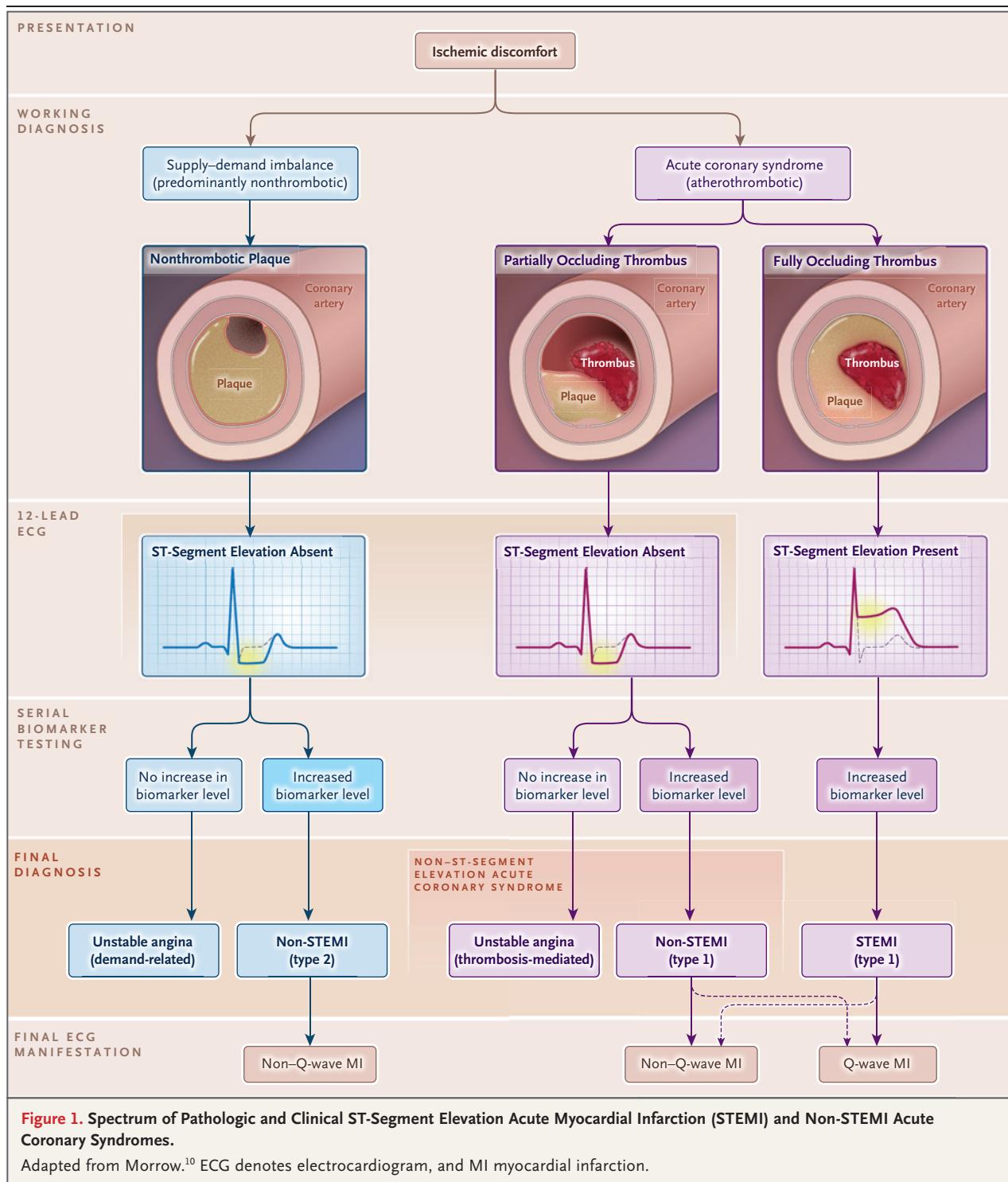
#### INITIAL MEDICAL EVALUATION, DIAGNOSTIC TRIAGE, AND RISK STRATIFICATION

Patients with acute myocardial infarction may present with typical ischemic-type chest discomfort or with dyspnea, nausea, unexplained weakness, or a combination of these symptoms (see the Supplementary Appendix.) If an acute coronary syndrome is suspected, the patient should be referred immediately to an emergency department for evaluation (American College of Cardiology–American Heart Association [ACC–AHA] class I recommendation, evidence level C).<sup>9</sup> A 12-lead ECG is obtained and evaluated for ischemic changes, with a goal of performing the evaluation in less than 10 minutes after the patient's arrival in the emergency department (ACC–AHA class I recommendation, evidence level C), and blood is sent for cardiac troponin testing (ACC–AHA class I recommendation, evidence level A). On the basis of the history and ECG, rapid diagnostic triage is performed, with the case classified as STEMI,<sup>8</sup> possi-

ble or probable acute coronary syndrome without ST-segment elevation,<sup>9</sup> or nonischemic chest pain; this addresses the first of six key management decisions (Table 1). Serial biomarker testing is performed to subclassify an acute coronary syndrome without ST-segment elevation as non-STEMI or unstable angina.

Serial measurement of cardiac troponin levels is the preferred biomarker method for differentiating non-STEMI from unstable angina and disorders other than acute coronary syndromes. In the appropriate clinical context, acute myocardial infarction is indicated by a rising or falling pattern of troponin levels, with at least one value above the 99th percentile of a healthy reference population (upper reference limit).<sup>1</sup> This rising or falling pattern has become increasingly important as more sensitive assays have been introduced.<sup>9</sup> High-sensitivity assays for troponin, which are currently available only outside the United States, increase diagnostic sensitivity and make it possible to effectively rule out myocardial infarction in 1 to 2 hours; these include assays that may rule out acute myocardial infarction after a single sample has been obtained.<sup>11</sup> However, such testing has decreased clinical specificity for acute myocardial infarction, since high-sensitivity assays detect the presence of troponin in most normal persons, and increased troponin levels are observed in a number of disorders other than acute myocardial infarction, including myocarditis and other causes of cardiac injury; cardiac, renal, and respiratory failure; stroke or intracranial hemorrhage; septic shock; and chronic structural heart disease.<sup>1</sup> With current troponin assays, concomitant measurement of creatine kinase MB or myoglobin levels, which is common practice, is redundant and no longer recommended (ACC–AHA class III recommendation, evidence level A).<sup>9,12</sup>

The initial risk assessment of a patient in whom an acute coronary syndrome is suspected should address two risks: the risk that the presenting syndrome is in fact an acute coronary syndrome, and if it is, the risk of an early adverse outcome.<sup>9,13</sup> The risk of an early adverse outcome is more closely linked to presenting features than to risk factors for coronary artery disease. Two validated models have been developed to assess this risk: the Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) models, which are available online and can be useful in initial patient care (ACC–AHA class IIa recommendation, evidence level B).<sup>9</sup>



## INITIAL MEDICAL CARE

## PREHOSPITAL CARE

Prehospital cardiac arrest and extension of necrosis are major factors in acute myocardial infarction—associated morbidity and mortality, making rapid initial assessment, initiation of treatment, and transportation to a hospital essential elements of initial care (see the Supplementary Appendix). ECG assessment by emergency medical services,

tion—associated morbidity and mortality, making rapid initial assessment, initiation of treatment, and transportation to a hospital essential elements of initial care (see the Supplementary Appendix). ECG assessment by emergency medical services,

**Table 1.** Six Initial Assessment and Management Decisions Pertaining to Patients Presenting with Chest Pain and a Possible Acute Coronary Syndrome.\*

1. Triage to an acute coronary syndrome pathway (STEMI, non-STEMI, possible or probable unstable angina, or nonischemic disorder) on the basis of the history, examination, ECG, and cardiac troponin test result.
2. Assess risk of cardiovascular death or recurrent ischemia (high, intermediate, or low risk) on the basis of clinical features, ECG, and troponin testing; an integrated risk score (e.g., TIMI or GRACE score) can be used.
3. Initiate general care: limit activity; administer aspirin, nitroglycerin, and a statin; consider administration of oxygen, beta-blocker, or morphine.
4. Choose invasive or noninvasive (ischemia-guided) initial strategy; the choice of early invasive management is based on risk and patient's preferences.
5. Select a second antiplatelet agent to add to aspirin (P2Y<sub>12</sub> inhibitor or glycoprotein IIb/IIIa inhibitor), with selection based on thrombotic risk, timing of invasive strategy, likelihood of need for surgical revascularization, and risk of bleeding.
6. Choose an anticoagulant agent (unfractionated heparin, low-molecular-weight heparin, fondaparinux, or bivalirudin) according to the initial management strategy (invasive or noninvasive) and risk of bleeding.†

\* ECG denotes electrocardiogram, GRACE Global Registry of Acute Coronary Events, STEMI ST-segment elevation acute myocardial infarction, and TIMI Thrombolysis in Myocardial Infarction.

† Fondaparinux is not approved for the treatment of acute coronary syndromes in the United States.

with communication of a STEMI diagnosis to the receiving hospital and preferential transport to a hospital with the facilities and expertise to perform PCI, results in more rapid performance of primary PCI and superior clinical outcomes.<sup>8,14,15</sup> This strategy can save approximately 15 minutes but at a cost, since the rate of false activation of a STEMI protocol is as high as 36%.<sup>16,17</sup> The ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery) trial tested prehospital administration of ticagrelor, which inhibits the P2Y<sub>12</sub> receptor, in patients with STEMI.<sup>18</sup> The treatment was safe but did not improve pre-PCI coronary perfusion. Two randomized trials of prehospital induction of therapeutic hypothermia in resuscitated patients with out-of-hospital cardiac arrest and initial ventricular fibrillation showed that rapid, large-volume infusions of cold fluids administered by paramedics modestly decreased core temperature at the time of arrival at the hospital but did not improve outcomes at discharge, as compared with in-hospital cooling.<sup>19,20</sup>

#### EMERGENCY DEPARTMENT AND EARLY INPATIENT CARE

The initial management of acute coronary syndromes includes bed rest with ECG monitoring and prompt initiation of antithrombotic therapy.

The severity of the symptoms dictates other features of general care (Table 2). Although the routine use of oxygen supplementation is still widespread, current evidence does not support its benefit in patients with normal oxygen levels. Hence, its use is recommended only for patients with hypoxemia (oxygen saturation <90%), respiratory distress, or other risk factors for hypoxemia (Table 2).<sup>8,9</sup> A large, randomized trial of oxygen supplementation in 6650 patients with acute myocardial infarction (DETO2X-AMI [Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction]) is under way (ClinicalTrials.gov number, NCT01787110).

Sublingual nitroglycerin is initially indicated for relief of ischemic discomfort and may be followed by intravenous therapy for ongoing ischemic discomfort, congestive heart failure, or uncontrolled hypertension. The approach to beta-blocker therapy is subject to debate, but overall, its use is favored, with initiation during the first 24 hours after admission.<sup>8,9</sup> Oral administration is generally safe, with intravenous therapy reserved for unrelieved hypertension. Beta-blockers should be avoided if the patient has risk factors for cardiogenic shock. Initiation or continuation of high-intensity statin therapy is based on favorable pleiotropic as well as cholesterol-lowering effects and on improvements in cardiovascular outcomes.<sup>9</sup> In addition, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers have a role in the treatment of acute coronary syndromes, especially in patients with anterior acute myocardial infarction, ventricular dysfunction, or heart failure. In the absence of contraindications, such therapy is begun within 24 hours after admission.<sup>8,9,13</sup> A fraction of patients who have had an acute myocardial infarction also become candidates for aldosterone inhibitors (ACC-AHA class I recommendation, level of evidence A).<sup>8</sup> Additional considerations apply in patient groups of special interest (see the Supplementary Appendix).

#### SELECTION OF A MANAGEMENT STRATEGY

General management algorithms for STEMI and acute coronary syndromes without ST-segment elevation are shown in Figure 2.

#### TREATMENT OF STEMI

Emergency reperfusion of ischemic myocardium that is in the process of becoming infarcted is the

**Table 2. Approach to Pharmacotherapy in Early Hospital Care of Patients with an Acute Coronary Syndrome without ST-Segment Elevation.\***

Therapeutic Target	Intervention
Myocardial supply–demand mismatch	Oxygen: Administer supplemental oxygen only if oxygen saturation <90%. Analgesics: Intravenous morphine (1 to 5 mg; may repeat in 5 to 30 min if necessary) may be reasonable for persistent ischemic pain. Nitrates: Administer sublingual nitroglycerin (0.3 to 0.4 mg; may repeat in 5 min, two times, as needed) for ischemic pain and intravenous nitroglycerin for persistent ischemia, heart failure, or hypertension. Beta-blockers: An oral beta-blocker should be started in the first 24 hr if there is no heart failure, low-output state, risk for shock, or other contraindication.† Calcium-channel blockers: A calcium-channel blocker (nondihydropyridine) should be used for persistent ischemia when beta-blockers are not successful, are contraindicated, or have unacceptable side effects.‡
Coronary thrombus	Antiplatelet therapy: Administer oral aspirin (initial dose, 162 to 325 mg; then 81 to 325 mg daily indefinitely) and a P2Y <sub>12</sub> inhibitor. Anticoagulant therapy: Administer an intravenous anticoagulant agent to all patients, regardless of treatment strategy.
Unstable atheroma or disease progression	Statin therapy: Initiate or continue high-intensity oral statin therapy (40 to 80 mg atorvastatin or 20 to 40 mg rosuvastatin on admission and then daily) for cholesterol management. ACE inhibitor: ACE inhibitors should be started in all patients with LVEF of <0.40 and in those with hypertension, diabetes mellitus, or stable chronic kidney disease; ACE inhibitors may also be reasonable in all other patients with cardiac or other vascular disease.

\* The recommendations are adapted from Amsterdam et al.<sup>9</sup> The approach to general treatment measures is similar for STEMI, although calcium-channel blockers are only weakly recommended for patients for whom beta-blockers are associated with unacceptable adverse events. The recommendation is class I for all listed interventions except analgesics and some uses of angiotensin-converting-enzyme (ACE) inhibitors, which are both class IIb; ACE inhibitors are class I in all patients with a left ventricular ejection fraction (LVEF) of <0.40 and in those with hypertension, diabetes mellitus, or stable chronic kidney disease and class IIb in all other patients with cardiac or other vascular disease. See Amsterdam et al.<sup>9</sup> and Anderson et al.<sup>13</sup> for additional information about dosages.

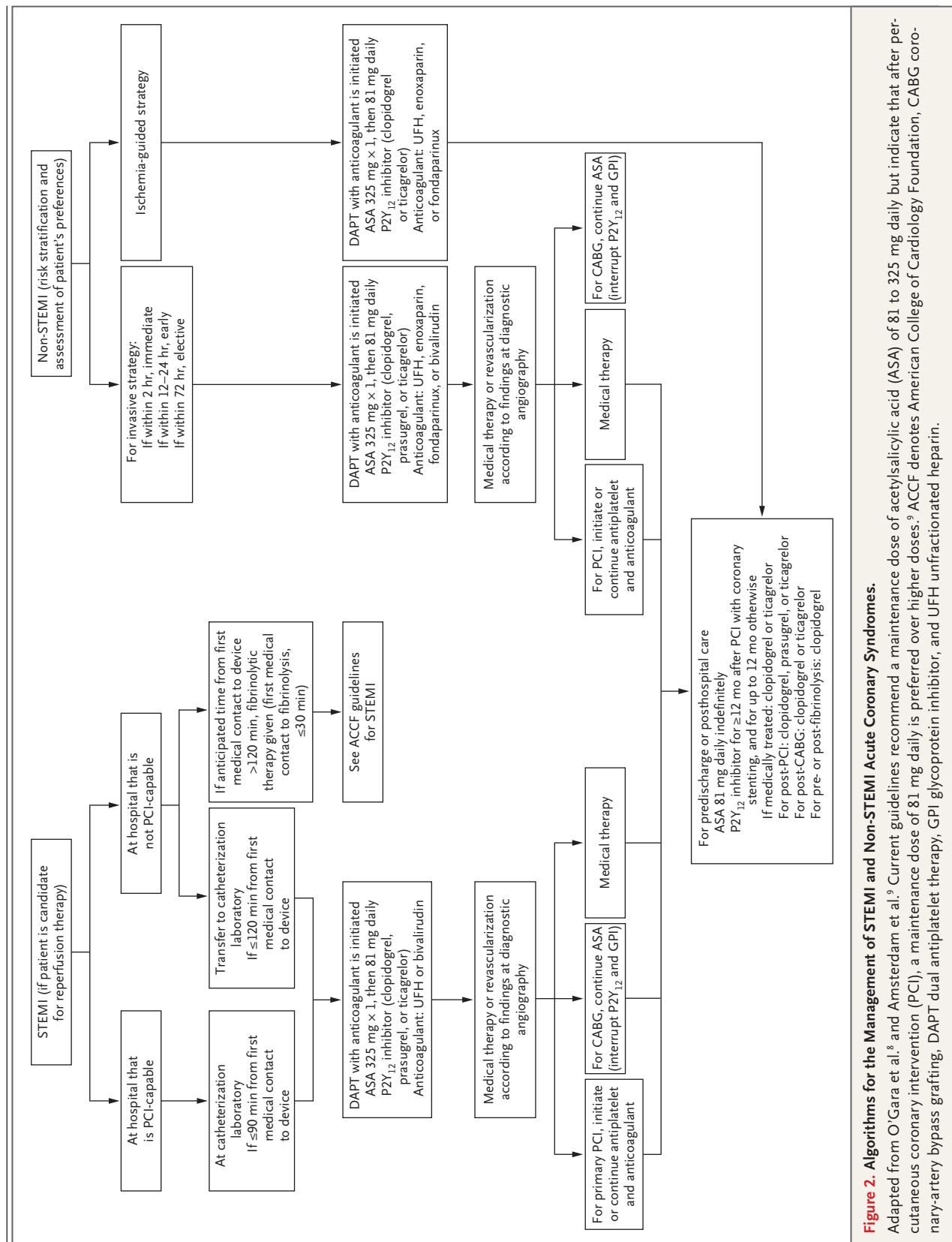
† Beta-blockers also reduce the incidence of tachyarrhythmias. Patients with initial contraindications to beta-blockers should be reassessed for eligibility.

‡ Contraindications to calcium-channel blockers include left ventricular dysfunction, an increased risk of cardiogenic shock, a PR interval of more than 0.24 seconds, and second- or third-degree atrioventricular block in a patient without a cardiac pacemaker.

most important advance in the treatment of STEMI over the past three decades and is the primary therapeutic goal. Coronary reperfusion is accomplished by means of primary PCI (angioplasty and stenting) or intravenous fibrinolytic therapy. Prompt PCI (with a performance goal of ≤90 minutes from the first medical contact) is the preferred approach at PCI-capable hospitals for STEMI with onset of symptoms within the previous 12 hours (ACC–AHA class I recommendation, evidence level A) and for STEMI with cardiogenic shock, regardless of the timing (ACC–AHA class I recommendation, evidence level B).<sup>8</sup> The advantages of primary PCI over fibrinolysis include lower rates of early death, reinfarction, and intracranial hemorrhage. However, when PCI is delayed by more than 120 minutes, fibrinolytic therapy should be given if it is not contraindicated (ACC–AHA class I recommendation, evidence level A), followed by routine consideration of transfer in the following 3 to 24 hours to a PCI-capable facility (ACC–AHA

class IIa recommendation, evidence level B).<sup>8</sup> With broad application of reperfusion therapy for STEMI, 30-day mortality rates have progressively declined from more than 20% to less than 5%.<sup>21</sup>

The recent evolution in the treatment of acute myocardial infarction largely involves management in the catheterization laboratory. Implantation of either drug-eluting or bare-metal stents is supported by STEMI guidelines.<sup>8</sup> Second-generation drug-eluting stents have assumed a dominant role in PCI. A 2013 network analysis that included 22 trials and a total of 12,548 patients with STEMI showed evidence of steady improvement in outcomes in association with the move from bare-metal stents to first-generation and then second-generation drug-eluting stents.<sup>22</sup> Cobalt chromium everolimus-eluting stents had the most favorable safety and efficacy profile, with reduced rates of cardiac death, acute myocardial infarction, and stent thrombosis, as compared with bare-metal stents.



**Figure 2. Algorithms for the Management of STEMI and Non-STEMI Acute Coronary Syndromes.**

Adapted from O'Gara et al.<sup>8</sup> and Amstel et al.<sup>9</sup> Current guidelines recommend a maintenance dose of acetylsalicylic acid (ASA) of 81 to 325 mg daily but indicate that after percutaneous coronary intervention (PCI), a maintenance dose of 81 mg daily is preferred over higher doses.<sup>9</sup> ACCF denotes American College of Cardiology Foundation, CABG coronary-artery bypass grafting, DAPT dual antiplatelet therapy, GPI glycoprotein inhibitor, and UFH unfractionated heparin.

An ongoing controversy in the use of PCI for STEMI is the approach to stenoses in nonculprit coronary arteries.<sup>23</sup> PCI of nonculprit stenoses has been contraindicated on the basis of observational studies, which are subject to selection bias. More recently, three randomized trials with samples of intermediate size (296 to 627 patients) showed reductions in ischemia-driven revascularization and variable effects on the risks of recurrent myocardial infarction and death with PCI of nonculprit stenoses.<sup>24-26</sup> A 2015 systematic review of five trials involving a total of 1568 patients confirmed a decreased risk of repeat revascularization (relative risk, 0.36; 95% confidence interval [CI], 0.27 to 0.48) and a lower risk of nonfatal myocardial infarction (relative risk, 0.58; 95% CI, 0.36 to 0.93), with an uncertain effect on the risk of death (relative risk, 0.82; 95% CI, 0.53 to 1.26).<sup>27</sup> On the basis of this evidence,<sup>24-27</sup> PCI of nonculprit lesions may be considered either at the time of primary PCI in hemodynamically stable patients or as a staged procedure (ACC–AHA class IIb recommendation, level of evidence B).<sup>23</sup> Larger multicenter, randomized trials are needed, including trials comparing staged versus immediate PCI of nonculprit arteries; one such trial, COMPLETE (Complete vs. Culprit-Only Revascularization to Treat Multi-Vessel Disease after Primary PCI for STEMI), is ongoing (NCT01740479).

Although early data favored manual thrombus aspiration during primary PCI,<sup>28</sup> data from more recent trials have not.<sup>29-31</sup> In the largest trial (involving 10,732 patients), manual aspiration had no significant effect on the risk of death from cardiovascular causes, myocardial infarction, or severe heart failure at 180 days, as compared with conventional PCI (without aspiration thrombectomy) (hazard ratio, 0.99), and the risk of stroke at 30 days was higher with manual aspiration (0.7% vs. 0.3%).<sup>30</sup> Similarly, in a meta-analysis of 17 trials involving 20,960 patients, aspiration thrombectomy was not shown to be of benefit in reducing the risk of death or reinfarction (hazard ratio, 0.90;  $P=0.11$ ).<sup>31</sup> Currently, the routine use of thrombus aspiration during PCI is not indicated, and selective use is viewed as poorly founded (ACC–AHA class IIb recommendation, evidence level C).<sup>23</sup>

In response to adverse outcomes associated with bleeding complications of PCI, radial-artery access has been advocated for coronary angiography and PCI,<sup>32</sup> particularly for patients with STEMI, in whom bleeding at the access site is

most common. A meta-analysis of 12 randomized trials comparing transradial with transfemoral PCI for the treatment of STEMI showed that radial access was associated with lower rates of access-site bleeding (2.1% vs. 5.6%), major bleeding (1.4% vs. 2.9%), and death (2.7% vs. 4.7%), despite a procedure time that was 2 minutes longer.<sup>33</sup> The most recent and largest trial randomly assigned 8404 patients with either STEMI or non-STEMI to radial or femoral access.<sup>34</sup> Radial access was associated with a reduction in the rate of adverse clinical events at 30 days, driven by decreases in deaths and major bleeding events, and was beneficial for both types of acute myocardial infarction.<sup>34</sup> One challenge to rapid adoption of the radial approach in general practice is overcoming the learning curve for achieving the outcomes observed in clinical trials.<sup>32</sup>

#### TREATMENT OF ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION

Given residual perfusion in the ischemic zone in acute coronary syndromes without ST-segment elevation, the urgency of and approach to revascularization differ from that in STEMI. Once a definite or likely diagnosis of an acute coronary syndrome without ST-segment elevation has been made, the patient is triaged to either an invasive strategy or an ischemia-guided strategy (i.e., an initial medical strategy with angiography reserved for evidence of spontaneous or provoked ischemia).<sup>9</sup>

An invasive strategy leads to improved outcomes and is favored for the majority of patients; the urgency of angiography (performed with the goal of revascularization) depends on the presence or absence of high-risk features (Table 3). If initial medical therapy stabilizes the patient's hemodynamic condition and relieves ischemic discomfort, angiography can proceed within 12 to 24 hours. An even more delayed approach (with angiography performed within 25 to 72 hours) is an option for patients at lower immediate risk.<sup>9,35</sup> In patients whose condition is unstable, urgent PCI is performed, as it is for patients with STEMI.

An ischemia-guided strategy is chosen for patients at low risk for recurrent ischemia (especially for women at low-risk and others for whom angiography carries excessive risk), for patients at hospitals where interventional services are unavailable, and on the basis of the patient's or physician's preference. Fibrinolytic therapy may be harmful

**Table 3.** Invasive and Ischemia-Guided Intervention Categories in Patients with Non-STEMI Acute Coronary Syndromes.\*

Variable	Invasive Intervention†			Ischemia-Guided Intervention
	Immediate	Early	Delayed	
Timing	Within 2 hr	Within 24 hr	Within 25–72 hr	Depends on spontaneous or provoked ischemia
Indications	Refractory angina, new-onset heart failure, new or worsening mitral regurgitation, recurrent angina during maximal medical therapy	High risk (e.g., GRACE score >140), rising troponin level, new ST-segment depression	Intermediate risk (e.g., GRACE score of 109–140, TIMI score of ≥2), ejection fraction <40%, postinfarction angina, diabetes, renal insufficiency, prior CABG, recent PCI (within 6 mo)	Low risk (e.g., TIMI score of 0 or 1); low-risk and troponin-negative women, patient's or physician's preference in absence of high-risk features, unavailability of interventional facilities or expertise

\* Data are adapted from Amsterdam et al.<sup>9</sup>

† Invasive interventions are those involving coronary angiography with the intention to perform percutaneous coronary intervention (PCI) or to refer the patient for CABG (coronary-artery bypass grafting), as appropriate.

in patients who have an acute coronary syndrome without ST-segment elevation and is therefore contraindicated. At the time of angiography, PCI is the most common intervention, but depending on the coronary anatomy and clinical features, a decision may be made to perform CABG instead of PCI or to forgo an intervention. Nonculprit arteries may be approached with the same cautions as for nonculprit arteries in patients with STEMI. Indeed, because the culprit artery may be difficult to identify with certainty in patients who have an acute coronary syndrome without ST-segment elevation, simultaneous multivessel PCI is often performed if the patient is hemodynamically stable.

#### ANTITHROMBOTIC THERAPY

Given the critical role of coronary thrombosis in the precipitation of acute myocardial infarction, antithrombotic therapy has assumed a cardinal role in the management of acute coronary syndromes.<sup>36</sup>

#### ANTIPLATELET AGENTS

Non-enteric-coated aspirin, at a dose of 162 to 325 mg, is recommended at the time of the first medical contact for all patients with an acute coronary syndrome (ACC–AHA class I recommendation, evidence level A).<sup>8,9</sup> The initial dose is followed by a daily maintenance dose of 81 to 325 mg of aspirin, which is given indefinitely (ACC–AHA class I recommendation, evidence level A).<sup>8,9</sup> However, whereas an 81-mg maintenance dose of aspi-

rin is required with ticagrelor and is preferred with prasugrel, the dose with clopidogrel is uncertain. In the large CURRENT–OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Optimal Antiplatelet Strategy for Interventions) trial, which had a factorial design, patients with acute coronary syndromes were randomly assigned to either double-dose clopidogrel (600-mg loading dose on day 1, followed by 150 mg daily for 6 days and 75 mg daily thereafter) or standard-dose clopidogrel (300-mg loading dose and 75 mg daily thereafter) and either high-dose aspirin (300 to 325 mg daily) or low-dose aspirin (75 to 100 mg daily). A nominal advantage was observed for patients undergoing PCI per protocol who received double-dose clopidogrel plus high-dose aspirin for 1 week ( $P=0.03$  for interaction).<sup>37,38</sup> A large pragmatic trial is testing a daily maintenance dose of 81 mg versus 325 mg of aspirin for secondary atherothrombosis prevention (NCT02697916).

In addition to aspirin, an oral P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel, or ticagrelor) is recommended for all higher-risk patients. For patients with STEMI who are undergoing primary PCI, a loading dose should be given as early as possible or at the time of PCI, followed by a daily maintenance dose for at least 1 year (ACC–AHA class I recommendation, evidence level A).<sup>8</sup> Two randomized trials have failed to support routine upstream administration of prasugrel or ticagrelor before timely PCI for patients with acute coronary syndromes.<sup>18,39</sup> Whereas prasugrel and ticagrelor, which are more potent than clopidogrel, may be

preferred with primary PCI, clopidogrel is recommended in association with fibrinolytic therapy and is given after fibrinolytic therapy for a minimum of 14 days (ACC–AHA class I recommendation, evidence level A) and for a maximum of 1 year (ACC–AHA class I recommendation, evidence level C).<sup>8</sup> For an acute coronary syndrome without ST-segment elevation, clopidogrel or ticagrelor is indicated at the time of presentation for patients treated with either an early invasive strategy or an ischemia-guided strategy (ACC–AHA class I recommendation, evidence level B).<sup>9</sup> Prasugrel becomes an option for an acute coronary syndrome without ST-segment elevation that is being managed with an early invasive approach at the time of stenting (ACC–AHA class I recommendation, evidence level B). Ticagrelor and prasugrel are more effective than clopidogrel<sup>40,41</sup> and are generally preferred in patients who are not at high risk for bleeding (e.g., those without a history of stroke or transient ischemic attack) (ACC–AHA class IIa recommendation, evidence level B).<sup>9</sup> A large, ongoing trial (TAILOR-PCI [Tailored Antiplatelet Therapy Following PCI]; NCT01742117) is evaluating the use of pharmacogenetic testing at the time of PCI to improve ischemic outcomes with clopidogrel in patients with acute coronary syndromes or stable coronary artery disease. The efficacy of clopidogrel relies on its conversion (by the CYP2C19 enzyme) to its active metabolite. Patients in the pharmacogenetic group who have a reduced-function allele (CYP2C19 \*2 or \*3) are assigned to ticagrelor. The comparison group receives standard clopidogrel dosing.

Glycoprotein IIb/IIIa inhibitors, an older class of antiplatelet drugs given intravenously, have a more limited role in the treatment of acute coronary syndromes, but when needed, they can provide rapid onset of antiplatelet activity before the patient is taken to the catheterization laboratory or for prevention and treatment of periprocedural thrombotic complications. Cangrelor, a short-acting intravenous P2Y<sub>12</sub> inhibitor, has recently become available as an adjunct to PCI for reducing the risk of periprocedural ischemic events in patients who have not been pretreated with a P2Y<sub>12</sub> or a glycoprotein IIb/IIIa inhibitor. With its fast onset-offset actions, cangrelor is superior to clopidogrel when clopidogrel preloading has not occurred,<sup>42,43</sup> but cangrelor has not been compared with prasugrel, ticagrelor, or the glycoprotein IIb/IIIa inhibitors.<sup>36</sup>

## ANTICOAGULANT AGENTS

Administration of a parenteral anticoagulant agent (i.e., unfractionated heparin, enoxaparin, bivalirudin, or fondaparinux) is recommended for patients who present with an acute coronary syndrome (ACC–AHA class I recommendation, evidence level A).<sup>8,9</sup> Fondaparinux alone does not provide adequate anticoagulation to support PCI but is useful for medical therapy, especially if the risk of bleeding is high. Enoxaparin is somewhat more effective than unfractionated heparin, particularly in patients who are treated with a noninvasive strategy. During noninvasive management of an acute coronary syndrome, anticoagulants are administered for at least 2 days and preferably for the duration of hospitalization, up to 8 days, or until PCI is performed. Anticoagulants are typically discontinued after uncomplicated PCI.<sup>8,9</sup> A current controversy is the choice of bivalirudin versus heparin. Early trials showed that bivalirudin reduced the risk of major bleeding, as compared with heparin or enoxaparin plus a glycoprotein IIb/IIIa inhibitor.<sup>44,45</sup> However, in these trials, numerical increases in ischemic events were noted with bivalirudin, as well as increases in acute stent thrombosis in patients with STEMI.<sup>46</sup> In the HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Intervention) trial, which relegated glycoprotein IIb/IIIa inhibitors to bailout use and administered conservative doses of heparin, bleeding rates were similar and ischemic outcomes were reduced with heparin as compared with bivalirudin.<sup>47</sup> Complicating the interpretation of these findings are divergent findings in a Chinese study.<sup>48</sup> Matching the intensity and duration of anticoagulant therapy to the patient's risk profile appears to be more important than the anticoagulant choice.<sup>49</sup>

## COMBINED ORAL ANTICOAGULANT AND ANTIPLATELET THERAPY

On the basis of limited evidence and expert opinion, current guidelines recommend antiplatelet therapy combined with oral anticoagulant therapy with a vitamin K antagonist in patients with STEMI who have an elevated risk of atrial fibrillation, mechanical heart valves, venous thromboembolism, or hypercoagulable disorders. The guidelines state that the duration of triple therapy (e.g., a vitamin K antagonist and dual antiplatelet therapy with aspirin and clopidogrel) should be as short as possible, given the risk of increased

bleeding.<sup>9,50</sup> The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial, a single-center study involving 563 patients (28% of whom had acute coronary syndromes), showed that an oral anticoagulant plus clopidogrel without aspirin, as compared with an oral anticoagulant plus clopidogrel and aspirin, reduced the risk of clinical bleeding (hazard ratio, 0.36; 95% CI, 0.26 to 0.50) without an increase in thrombotic events.<sup>51</sup>

A more recent study, PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), involved 2124 patients with atrial fibrillation (50% of whom had acute coronary syndromes) who underwent PCI and stenting.<sup>52</sup> In the study, low-dose rivaroxaban (15 mg daily) plus a P2Y<sub>12</sub> inhibitor (primarily clopidogrel, at 75 mg daily), without aspirin, for 12 months or very-low-dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy for 1, 6, or 12 months, was compared with standard therapy (a vitamin K antagonist plus dual antiplatelet therapy for 1, 6, or 12 months). The rates of clinically significant bleeding were lower with either of the rivaroxaban regimens than with standard therapy (hazard ratio with the low-dose regimen, 0.59; 95% CI, 0.47 to 0.76; hazard ratio with the very-low-dose regimen, 0.63; 95% CI, 0.50 to 0.80;  $P<0.001$  for both comparisons). The rates of death from cardiovascular causes, myocardial infarction, or stroke were similar among the groups. This emerging database of accumulated evidence from clinical trials points to new options for improving clinical outcomes in patients with acute myocardial infarction who have indications for oral anticoagulant therapy.

#### COMPLICATIONS

The rates of major complications of acute myocardial infarction have declined dramatically with early reperfusion and current medical therapy.<sup>53</sup> Nevertheless, complications are a leading cause of death and deserve careful consideration (see details in the Supplementary Appendix).<sup>8,9,13,21</sup>

#### LATE INPATIENT AND PREDISCHARGE CARE

In the era of primary PCI, the duration of hospitalization is as short as 3 days for uncomplicated acute myocardial infarction, with observational studies suggesting that the outcomes for patients admitted to a step-down unit are similar to the outcomes of intensive care. During the later hospital phase, patients' activity is increased but continues to be closely monitored. Medical therapy is transitioned to oral medications that are appropriate for long-term outpatient use. Near the time of discharge, functional evaluations are undertaken, including echocardiography for left ventricular functional assessment and, in selected patients (e.g., patients treated with an ischemia-guided strategy), exercise stress testing. Education is provided about diet, activity, smoking, and other risk factors (e.g., lipids, hypertension, and diabetes); outpatient medical and secondary prevention therapies are reviewed; and follow-up planning occurs (Table S1 in the Supplementary Appendix). Important in discharge planning is referral to cardiac rehabilitation, which is an ACC–AHA class I recommendation (evidence level B) because of its favorable effects on outcomes.<sup>8,9,13</sup> Three large, randomized clinical trials are investigating whether potent regimens of antiinflammatory treatment with colchicine, methotrexate, or canakinumab can be effective as secondary prevention to reduce the risk of subsequent acute myocardial infarction (NCT02551094, NCT01594333, and NCT01327846).

#### FUTURE DIRECTIONS

Although the case fatality rates among patients with acute myocardial infarction have declined substantially, considerable opportunities for improvement remain. Care of patients with acute coronary syndromes has advanced remarkably over the past three decades and continues to evolve. Adherence to evidence-based guidelines for the care of such patients correlates with improved outcomes. Continued efforts aimed at improving the translation of evidence-based interventions into routine practice are essential.<sup>54</sup> Several new therapeutic approaches, such as reducing inflammation, mitigating reperfusion injury, inducing myocardial regeneration, and ameliorating adverse

remodeling, are under active investigation but, with the exception of ACE inhibition, have so far not proved beneficial in the acute care setting. Because of improved rates of short-term survival after acute myocardial infarction owing to contemporary management methods, subsequent development of heart failure is emerging as a prominent cause of longer-term illness and death. The very high mortality rate (>40%) among patients with cardiogenic shock after acute myocardial infarction remains a particular challenge in need of solutions. Acute myocardial infarction continues to have a major effect on national and global

health and remains a crucial target for scientific advancement in medicine.

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